Council for International Organizations of Medical Sciences

Third meeting of CIOMS Working Group (WG) XI:
Patient involvement in the development and safe use of medicines
1–2 May 2019, Geneva, Switzerland

Minutes (web)

Version 7 June 2019

1. Opening

Hervé le Louët (CIOMS President) welcomed the participants and commended them for the progress made in the lead-up to this meeting, which marks the mid-point of the Group's expected work span.

Lembit Rägo (CIOMS Secretary-General) added his words of welcome and thanked the participants for their contributions to the Open Meeting held on the previous day to gather wide input to the Group's work.

Meeting officers: The following WG members were selected:

- ***Co-chairs***: Elisabeth Oehrlein and Isabelle Moulon (Day 1 a.m.), Kerry Leeson-Beevers and Marilyn Metcalf (Day 1 p.m.), Kaisa Immonen and Theresa Mullin (Day 2 a.m.), and Nikos Dedes and Michael Richardson (Day 2 a.m.).
- ***Rapporteurs:*** Leo Russo (Day 1 a.m.), Ola Apara (Day 1 p.m.) and Stella Blackburn (Day 2); assisted by Monika Zweygarth.

Participants: There was a brief round of introduction. A list of participants is shown in **Annex 1**.

Agenda: The proposed meeting agenda was modified to have the general discussion on "Next steps" before the presentations of the current draft sections by the subgroup leads.

Previous meeting minutes: The minutes of the 2nd WGXI meeting (version of 22 November 2018, amended in line with comments received from WGXI members) were handed out at the meeting. No objections were raised to the minutes. It was noted that the public WG meeting minutes on the CIOMS website are appreciated by some readers.

2. Brief presentations on relevant recent initiatives

Feedback from the FDA/CTTI Public Workshop

(Theresa Mullin)

Presentation: As a follow-up to the FDA's Patient-Focused Drug Development meetings, the FDA and the Clinical Trials Transformation Initiative (CTTI) held a workshop on Incorporating Patient Perspectives in Clinical Trials on 18 March 2019. The workshop explored factors that may impact patients' participation in trials, such as: inclusion and exclusion criteria which some patients felt bore little relation to "real-life" patients, patients' willingness to participate, timing and convenience issues, and limitations to sharing of results with patients e.g. due to blinding requirements. Patients also commented that more use of information from medical records should be used to prevent repeated questions, likewise existing recent blood results. A public report will be made available.

Discussion: participants highlighted the need for trusted information on clinical trials to which patients can be directed (echoed in the report on a survey conducted by the Dutch Clinical Research Foundation, DCRF). The problem of concealed participation in multiple trials for financial reasons was mentioned; however, it was determined that this is outside the scope of the WGXI report. The WGXI will consider including some of the learnings from the FDA/CTTI initiative in its guidance, e.g. as a case study in an appendix.

EMA initiatives on involving young people

(Isabelle Moulon, François Houÿez)

Presentation: The European Medicines Agency (EMA) is working towards more involvement of young people in its activities, on the basis of the Principles on the involvement of young patients/consumers developed by the Agency. These working principles set out best practice for the interaction between scientific committees and young people under 18 years old. They also address issues such as obtaining parental consent, protection of personal data and the privacy of the young patients. They define what input young people could contribute and suggest options on how best to capture their perspectives. They also establish a process for identifying, supporting and consulting with young people. Involving young people in the Agency's activities is considered on a case-by-case basis when it is expected that their views could enhance scientific discussions related to the development and assessment of medicines.

Isabelle gave some examples of how this was done in practice.

Discussion: The WG members discussed issues of involving parents or legal guardians, the challenges of setting age limits for involvement of children (EMA doesn't set age limits), and language barriers resulting in a possible selection bias. In the WGXI guidance it may be useful to define population groups requiring special consideration such as children and pregnant women. The WG also discussed logistical considerations when seeking advice and experience from paediatric patients in advisory committees, for example by whom they were accompanied and whether expenses were reimbursed.

3. Reflections from the Open Meeting on Patient Involvement

In a "Tour de table" the meeting participants gave their feedback on the Open Meeting on Patient Involvement held on the previous day. The following topics were mentioned (in descending order of frequency):

- ***Need for a global guidance*** for people in all parts of the world (*"It's a whole world out there not operating to the same understanding"*). The guidance should recognize diversity, and should be free of cultural bias.
- ***Who is "the patient", and how can fair representation be achieved?*** There are many groups, and some are more active than others. For example, patients with diseases of

poverty, depression or chronic conditions of old age are not well represented. The stigma of some diseases may also prevent patient involvement.

- ***The Open Meeting was useful*** and achieved its purpose of sharing the group's work and gathering input.
- ***Practical guidance*** is needed on "what stakeholders should do" to achieve meaningful patient involvement. The guidance should recommend principles but also show that there is no one-size-fits-all approach.
- ***Transparency and conflict of interest*** turned out to be important topics. It was emphasized that conflict of interest is not just financial but could include intellectual, politics, religion, own research and career concerns.
- ***Need for an easy-to-read guidance*** that will be accessible to a broad audience. E.g. there should be a stand-alone summary for each chapter.
- ***Access to medication*** is important, and this should be recognized in the guidance (*"If a drug doesn't become available then our work is in vain"*).
- ***Managing expectations***: Cultural changes within organizations happen gradually.
- ***Aspirational recommendations:*** The guidance can include "trend-setting" recommendations, and these should be distinguished from recommendations for current best practice.
- ***The roles of different health professionals*** should be considered. Not only doctors, but also nurses and pharmacists communicate with patients, especially in resource-limited settings.
- ***Patient data*** were an important theme; guidance is needed on how to obtain and use these appropriately.
- ***The patient's treatment cycle*** is not the same as the life cycle of a medicine.
- ***Buy-in from stakeholder groups*** will help in disseminating /implementing the guidance.
- ***Definitions:*** Some terms (e.g. "meaningful engagement/involvement") should be discussed in the text, not just defined in a glossary entry.

In the discussion that followed, it was suggested that the guidance should be limited to a feasible scope and should include a section on what it does not cover (e.g. certain aspects of the Health Technology Assessment discussion).

More input is expected at the DIA 2019 Global Annual Meeting, to be held on 23-29 June 2019 in San Diego, U.S., where Judy Zander has organized two CIOMS WGXI-related sessions[1].

Once the guidance is more mature CIOMS may reach out to Open Meeting participants to seek their comments.
It was also recommended that CIOMS develop a communication and dissemination plan for the guidance, to make sure it will reach a wide audience and particularly patients' advocates.

At the end of the WGXI meeting Lembit Rägo called for volunteers to write an article about the learnings from the Open Meeting. This would preferably be published in an open-access journal.

4. General discussion on how to proceed

The WG discussed how best to proceed in producing a solid guidance document and clarified some recurring questions.

Audience of the guidance: The intended audience includes the stakeholders represented in the WG, i.e. regulators, patient organizations, industry and pharmacovigilance organizations, as well as health professionals who provide frontline care and interact with patients on safe use of medicines and on clinical trials. The guidance is primarily addressed to people involved in policy-making. Not all sections will be equally relevant to all groups.

[1] #154, Current initiatives on Patient Involvement in the Medicinal Product Lifecycle (Monday 24 June, 3:30-4:30 pm), and #254.1 RT, Round table discussion (Tuesday 25 June, 2-3 pm)

Working Group composition: It was agreed to:

- revitalize efforts to have a health care professional representative in the Working Group
- seek input from digital technology specialists, as the guidance will need to address new technologies.

Working mode: All WGXI members are part of at least one drafting subteam ("workstream"). New members were asked to choose the subteams to which they will contribute. The team composition was confirmed at the end of the meeting.

The workstreams are following a managed approach to collaboration, with a workplan, timelines and regular conference calls. Changes in workstream composition will be minimized to maximize efficiency.

For each topic a main writer will be identified to produce a full draft, with input from others. At least one patient representative will contribute to each draft or review it.

Structure of the guidance: Some suggestions were made on how best to present information/evidence pertaining to different phases of patient involvement along the life cycle of medicines, and cross-cutting themes. The format will be revisited as the drafting progresses.

5. Presentation of current section outlines

During the meeting it was agreed to re-number the chapters as 1-9, rather than 1-4 and 5.1–5.5. The new numbering is used in these minutes.

The presentations are reflected here in the sequence of the chapters, although they were not given in that sequence: Chapter 5 was discussed on Day 1 a.m. due to travel time constraints, and Chapter 4 was discussed before chapters 1-3 on Day 1 at 3 p.m. by pre-scheduled teleconference.

Group 1

Chapter 1. Introduction
(Theresa Mullin)

The introduction will set the scene for the CIOMS guidance, explain why it is important and timely, and point to the topics covered in the guidance. It will not provide a summary; this will be given upfront in the book before the Introduction chapter.

- Work on this Chapter will be suspended until the other sections are more mature.

Chapter 2. Landscape of patient engagement, patients involved in regulatory initiatives
(Elisabeth Oehrlein)

This draft section has detailed information about patient involvement initiatives, with vignettes (examples) describing what has been achieved by regulatory authorities, patient organizations, inter-disciplinary initiatives, professional societies and health technology assessment bodies. It further includes a timeline of patient engagement, which will be reflected in an annex.

In the discussion it was suggested to make the timeline more balanced by including more information from outside the U.S. and Europe, and more information relating to the safe use of medicines. The timeline can serve as a reference list pointing to best practices and ongoing initiatives (e.g. PFMD, SYNaPsE). Possibilities to combine it with timelines given in other chapters (labelling) will be explored. The chapter should also highlight the roles of research funders and of journals in patient involvement.

Chapter 3. Patient Involvement in Advancing Treatments for their Disease
(Marilyn Metcalf)

This chapter describes the roles of the main stakeholders (patients, regulators, industry, health professionals) at each stage of the medicines life cycle.

It was suggested to:

- Add an "agenda-setting" stage at the beginning[2], to include information on identifying unmet needs and patient group partnerships with biotech organizations.
- Show that "monitoring" and "communication" extend along all life cycle stages.
- Add information about stakeholder roles in clinical trials, including patient involvement in ethics committees and institutional review boards (referencing the 2016 CIOMS/WHO Ethical Guidelines as relevant). The European AIDS Treatment Group (EATG) experience on clinical trials may be useful for this section.
- Under "Regulatory review", include basic concepts of benefit/risk assessment as a basis for decisions on product approval.
- Ensure a common understanding of terms upfront by pointing readers to definitions and explanations (e.g. "sponsors" in the regulatory sense, distinguishing between commercial and publicly-funded developers).

It was agreed to add a separate section on Challenges specific to low- and middle-income countries (LMIC).

Chapter 4. Guiding principles for engagement
(Charles Garrigan for Beverly Harrison, by teleconference)

This chapter looks at: core principles for Patient Engagement, building organizational capabilities ("culture change"), operational considerations, and why and how the value of patient engagement should be measured.

In the discussion, the following was suggested.

- Include the management of conflicts of interest both as a "Principle" and an "Operational consideration" – this emerged as a central topic at the Open Meeting.
- Make the chapter applicable to all stakeholders, beyond industry (reference work of PFMD and NHC, and the operational points of the Declaration of Helsinki)
- Provide actionable recommendations, with practical tools and templates (e.g. look at DIA's Patient-Centered Drug Development Toolkit)
- Provide high-level recommendations on how to measure the value of patient involvement as conducted by different stakeholders.

Group 2

Chapter 5. Developing regulated information for patients about medicines: what is the role of patients?
(Meredith Smith)

This section covers patient involvement in (1) the development of labelling, (2) iterative pilot testing and (3) evaluation of information for patients about medicines on the market. The group has developed a full draft; a table comparing patient labelling in different jurisdictions will be added.

In the discussion the following was suggested:

- Discuss practical barriers and how to overcome them, e.g. linked to ethics and social science, (**N.B.: A section on "barriers" should also be included in other chapters as relevant**)

[2] Consider EUPATI's life cycle figure in: Guidance for patient involvement in industry-led medicines R&D.

- Metrics for high quality in patient labeling materials (e.g. the PEMAT tool on the AHRQ website, the BMS Universal Patient Language)
- Recommend patient involvement at an early stage. This could be linked to consent in clinical trials. However, it is not easy to determine when is the right time to involve patients as this may depend on the likelihood and timing of regulatory approval. This point requires further discussion with other stakeholders.
- Consider the context in different parts of the world. For example:
    - In Africa, patients rarely receive package inserts, and the medicines are often not dispensed in their original packaging. In some areas, literacy may be an issue. Health professionals dispensing medicines, including pharmacists and nurses, therefore have an important role in the safe use of medicines.
    - In the U.S. direct-to-consumer advertising is permitted, affecting the credibility of patient leaflets as they may be perceived as promotional.
- Point to best practices in using additional channels to inform patients about medicines, as the label is heavily regulated (example: the government-sponsored medical information space in the Netherlands).
- Propose innovative ideas, e.g. uses of digital technologies to provide tailored information based on patient profiles.

Chapter 6. Patient involvement in the development, implementation and evaluation of additional risk minimisation measures
(Cheryl Renz)

The topics to be covered in this chapter include: (1) concepts of risk minimisation, (2) the measures used i.e. “routine” risk minimisation such as labelling, packaging, and additional risk minimisation measures (aRMMs), and (3) approaches to patient involvement in the development, implementation and effectiveness evaluation of these measures, except for labelling, which is covered in Chapter 5. The chapter will include a regulatory overview on the evolution of additional risk minimisation. It will also consider practical barriers and proposed solutions, including early implementation of tools in clinical trials.

In the discussion it was suggested that this chapter should:

- Consider that medicines are taken in different life contexts, affecting risk minimisation;
- Discuss management of risks not subject to a formal aRMM;
- Discuss the role of informal caregivers other than legal guardians, e.g. family of patients with psychiatric conditions;
- Reflect on ethics of risk minimisation; and
- Explain the concepts in clear, simple language and possibly include a case study.

Chapter 7: Patient involvement in the generation of safety data
(Leo Russo)

This chapter outlines where patients are involved in generating data – both “primary” data collected as part of formal studies, and “secondary” data collected during routine health care - and how these data are used on their behalf. Patients should have a say in what happens to their data; their privacy and confidentiality should be ensured. Patients should have access to their own data, as well as the outcomes of analyses based on them.

In the discussion it was suggested that the chapter should:

- Introduce the different data types, including “primary” data collected in studies, and “secondary” data collected for other purposes e.g. in electronic health records
- Use of data from expanded access/compassionate use programmes
- Focus on the use and limitations of “real-world data” (identifying and defining an appropriate term), and the need to validate the quality of such data

- Special challenges of protecting data confidentiality in treatment and monitoring programmes in resource-limited settings
- How analysis of patient-generated data may result in better quality of life for patients and may also identify specific risk factors to enable choices to be made.

Chapter 8: Patient involvement in developing crisis/time-bound communications
(Michael Richardson)

This chapter relates to patients' involvement in developing and disseminating urgent communications that need to be disseminated quickly (i.e. within days). It provides guidance on how to convey clear messages on actions to be taken by health care professionals and patients, and how to deal with any follow-up communications that might be needed. In addition to regulators, trusted patient organization can be instrumental in disseminating such messages, provided they are given adequate resources for this purpose.

In the discussion it was suggested to:

- Include a list of the most relevant references;
- Include case studies on confusing messages and how to avoid them (e.g. from the NHC Working Group on Communication); and
- Discuss the role of patient organizations in proactively reducing distress that may be caused by an impending crisis (e.g. non-availability of thyroid medicines).

6. Group work

Groups 1 and 2 worked separately in breakout sessions to agree on next steps in developing the draft chapters further, in line with the suggestions made during the plenary sessions.

7. Feedback from break-out sessions

The workstream leads reported back on the discussions and next steps agreed during the breakout sessions. The composition of the drafting teams was confirmed.

8. Glossary / definitions

In defining terms the group will look at existing CIOMS terms, other organizations' glossaries (e.g. EMA, FDA; EUPATI). It was proposed to:

- Explain important terms not only in the glossary, but also when they are first introduced in relevant chapters. This applies especially to difficult terms (e.g. "meaningful patient engagement/involvement"), and those which may have special connotations for certain readers (e.g. "Sponsor").
- Use a single term for a given concept throughout the guidance, and list equivalent terms used in other jurisdictions in the glossary.
- Avoid terms that have a technical and a lay meaning (e.g. "safe use").

9. Conclusions and agreement on next steps

The drafting sub-teams will send the CIOMS Secretariat their revised drafts by 20 September, to be circulated to the full Working Group for review before the 4th Working Group Meeting.

Date of next meeting: The 4th Working Group meeting is planned to be held in the second half of October 2019. The date and venue remain to be confirmed.

10. Closure

In closing the meeting, Lembit Rägo thanked the participants for their contributions. The group now has a clearer vision of how the CIOMS guidance can complement other existing guidance on patient involvement.

Annex 1: List of participants

* = new participant

CIOMS	Lembit **Rägo**	Secretary-General
	Panos **Tsintis**	Senior Advisor
	Monika **Zweygarth**	Technical writer
WHO	Shanthi **Pal**	Safety and Vigilance Team (SAV)
Patient representatives	Nikos **Dedes**	European AIDS Treatment Group (EATG)
	Francois **Houÿez**	European Organisation for Rare Diseases (EURORDIS)
	Kaisa **Immonen**	European Patients' Forum (EPF)
	Regina **Kamoga**	International Alliance of Patients' Organizations (IAPO)/Community Health and Information Network (CHAIN)
	Kerry **Leeson-Beevers**	Alström Syndrome UK
	Elisabeth **Oehrlein**	National Health Council, U.S. (alternate for *Marc Boutin)
Regulators	Ton **De Boer**	Medicines Evaluation Board (MEB), the Netherlands – (alternate for Sabine Straus)
	*Talia **Lacroix**	Health Canada
	*Yusuke **Matsunaga**	Pharmaceuticals and Medical Devices Agency (PMDA)
	Isabelle **Moulon**	European Medicines Agency (EMA)
	Theresa **Mullin**	U.S. FDA
	*Ken **Sakushima**	Pharmaceuticals and Medical Devices Agency (PMDA)
	Almath **Spooner**	Health Products Regulatory Authority (HPRA)
	*Annemiek **van Rensen**	Medicines Evaluation Board (MEB), the Netherlands (second alternate for Sabine Straus)
	Judy **Zander**	U.S. FDA
All stakeholders / Pharmacovigilance	Brian **Edwards**	International Society of Pharmacovigilance (ISOP) (alternate for Sten Olsson)
	Linda **Härmark**	Netherlands Pharmacovigilance Centre Lareb
	Marie **Lindquist**	Uppsala Monitoring Centre (UMC)
	*Peter **Pitts**	Center for Medicine in the Public Interest (CMPI)
	Theo **Raynor**	Leeds University, U.K. (retired)
Industry	*Leanne **Angst-Wu**	Roche
	Olatayo **Apara**	Takeda
	Stella **Blackburn**	IQVIA
	Matthias **Boedding**	Merck
	Charles Garrigan, for Beverly **Harrison**	(on Day 1, by phone) Janssen
	Marilyn **Metcalf**	GSK
	*Rebecca **Noel**	Eli Lilly
	Cheryl **Renz**	AbbVie
	Michael **Richardson**	Bristol-Myers Squibb
	Leo **Russo**	Pfizer
	Meredith **Smith**	Amgen Inc.
	*Christine **Stürchler**	Novartis
Apologies		
Patient representatives	Sonja **Potenze**	International Alliance of Patients' Organizations (IAPO)
Regulators	Mick **Foy**	MHRA, United Kingdom
	Martina **Schäublin**/ Dirk **Essers**	Swissmedic
Health care professionals	Christian **Thomeczek**	World Medical Association
Industry	Beverly **Harrison**	Janssen
	Stephen **Heaton**	Bayer AG
	Ravi **Patel**	United Therapeutics
